Reprinted from ANNALS OF INTERNAL MEDICINE Vol. 128; No. 9, 1 May 1998
Printed in U.S.A.

Cancer Prevention: Better Late than Never?

The historical view of cancer etiology has been that the latent period between a carcinogenic exposure and the diagnosis of this disease is typically quite long. This impression has been fueled by numerous epidemiologic studies, including those of occupational cancer (for example, one review reported a 35-year mean difference between asbestos exposure and mesothelioma [1]), radiogenic cancer (another study indicated that excess cases of cancer were still occurring in Japanese survivors of the atomic bomb 40 years later [2]), and early-life risk factors for breast cancer (most studies have found that ages at menarche and first live birth were risk factors [3]).

This perspective was further supported by results from bioassays of carcinogens in a study of laboratory animals. In a review (4), inverse relations between dose and duration of the latent period were frequently noted; even high-dose exposures were often associated with latency periods that involved a considerable percentage of the animal's expected life span. As a result of these observations and other studies, clinicians and the general public developed a certain sense that cancer prevention efforts for middle-aged and elderly persons (in whom the disease takes its greatest toll) were futile.

In the research community, this view has shifted incrementally and, ultimately, radically during the past 25 years on the basis of accumulating epidemiologic and laboratory evidence. Early in this period, excess risks for lymphoma related to immunosuppressive drug use (5) and risks for endometrial cancer related to hormone replacement therapy (6) were noted to appear shortly after initiation of treatment and to decline or disappear rapidly after cessation of treatment. Detailed studies of cigarette smokers revealed meaningful declines in risk for lung (7) and bladder (8) cancer within a few years of smoking cessation, even among persons who had smoked hundreds of thousands of cigarettes.

These studies were followed by others indicating that high intake of fruits and vegetables in middle-aged and older persons was linked with a reduced risk for several epithelial tumors (9) and by studies that found a close temporal association between infection with human papillomavirus and development of cervical dysplasia (10). Most recently, two exposures occurring in the 10 years before diagnosis of breast cancer—hormone replacement therapy (11) and weight loss (12)—have been linked to an excess risk and a protective effect, respectively. These findings are particularly notable because breast cancer has been the cancer for which the impression that risk is established decades before disease onset has been most profound.

In concert with these and many other epidemiologic observations, advances in molecular biology and studies of premalignant lesions have also altered our perceptions of temporal factors in carcinogenesis. Gone are the concepts of "initiation" and "promotion"; these have been replaced by "multistage carcinogenesis." It is now recognized that many somatic events must often occur before a replicating tissue accumulates enough critical genetic damage to push it from a normal phenotype to a premalignant one, from a premalignant state to a malignant one, and from a localized tumor to a metastatic one (13). Many of the required genetic changes can happen late in the process, very close in time to the clinical manifestation of disease. Although some of these late events can result simply from genomic instability caused by earlier events, many may be caused or prevented by specific exposures occurring late in the process. As a result of these population and laboratory findings, considerable research efforts (including several clinical trials) and substantial public health enthusiasm are now focused on preventive interventions throughout life.

The study reported by Grodstein and colleagues in this issue (14) adds to the accumulating evidence that "late" exposures may influence cancer risk and, as a result, adds to the enthusiasm for interventions that may result in rapid risk reduction. In this study, 59 000 postmenopausal nurses were followed for up to 14 years to examine the incidence of colorectal cancer in relation to use of hormone replacement therapy. Compared with the risk in women who had never used hormone replacement therapy, the risk was reduced by 35% in current users and by 30% in those who had stopped using hormone replacement therapy in the previous 5 years. No risk reduction was seen for women who had stopped receiving therapy 5 or more years before the questionnaire response. No evidence suggested an association between duration of use and risk reduction, either overall or in current users.

Information was also available for diagnoses of

This paper is also available at http://www.acponline.org.

colorectal adenoma. Overall, no association was seen with any measure of hormone use. For large adenomas (≥1 cm), however, the pattern was similar to that seen with colorectal cancer: protection, but only among current users. The authors concluded that estrogen is protective, but only at a late stage in carcinogenesis.

Can estrogen be added to the list of proven late-acting etiologic agents? Should drug companies consider adding prevention of colorectal cancer to the indications for use of hormone replacement therapy? Should clinicians add this as a known benefit to the complex discussion of risks and benefits with patients contemplating such therapy? The answer to all of these questions is no. Published studies are somewhat consistent: Most have shown a decreased risk for cancer with current or very recent hormone use, with no evidence of additional benefit with increased duration of use. However, the concern over this association, as for a plethora of other purported protective effects of hormone replacement therapy, is this very lack of the specificity of beneficial effects. With the notable exception of breast cancer, there is hardly a disease for which it has not been suggested that current use of hormone replacement therapy is preventive. Indeed, in one follow-up study, the rates for 11 of the 12 major categories of causes of death investigated, including infectious, neurologic, and respiratory diseases, were 12% to 86% lower among women using hormone replacement therapy (15). One exposure can certainly be related to several conditions, but it should be noted that the broader the spectrum of associations, the greater the concern that it is not the exposure itself that is responsible but rather the characteristics of the population exposed. Indeed, several studies have found that women who have received hormone replacement therapy, especially those who currently receive this therapy, differ from nonusers in a variety of ways (16, 17). Whether any differences could be responsible for the deficit of colorectal cancer is impossible to say. Because we know so little about the determinants of this tumor, we do not know which exposures to measure and control for. Resolution of these concerns will be difficult. Some help may come from a large randomized trial of hormone replacement therapy (18), but this trial may not be large enough to address the risk differences suggested for colorectal cancer. Clarification may also come from studies of populations for which the determinants of hormone replacement therapy use are consequentially different.

Given the increasingly widespread use of hormone replacement therapy, one hopes that this reported association will prove to be real and causal. Even if it doesn't, however, it reinforces our increasing realization that actions taken late, close in time to when cancer might develop clinically, can indeed be preventive. We clearly need to focus on young people in emphasizing a healthy lifestyle and eliminating carcinogenic and other toxic exposures. This is ultimately the best way to achieve a healthier, longer-lived society. For the mature members of the population, however, the prospect of being able to overcome some of the untoward consequences of the personal and societal indiscretions of our youth through more prudent actions now sounds awfully good.

Robert N. Hoover, MD, ScD
National Cancer Institute
Bethesda, MD 20892

Requests for Reprints: Robert N. Hoover, MD, ScD, National Cancer Institute, Epidemiology and Biostatistics Program, Room 433, 6130 Executive Boulevard, Bethesda, MD 20892.

Ann Intern Med. 1998;128:771-772.

References

1. **Selekoff IJ.** Cancer risk of asbestos exposure. In: Hiatt HH, Watson JD, Winston JA, eds. Origins of Human Cancer, v 4. New York: Cold Spring Harbor Laboratory; 1997:1765-84.
2. **Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al.** Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. Radiat Res. 1994;137(2 Suppl):517-67.
3. **MacMahon B, Cole P, Brown J.** Etiology of human breast cancer: a review. J Natl Cancer Inst. 1973;50:21-42.
4. **Hueper WC, Conway WD.** Chemical Carcinogenesis and Cancers. Springfield, IL: Charles C. Thomas; 1964.
5. **Hoover R, Fraumeni JF Jr.** Risk of cancer in renal-transplant recipients. Lancet. 1973;2:55-7.
6. **Weiss NS, English DR, Szekely DR, Schweid AI.** Endometrial cancer in relation to patterns of menopausal estrogen use. JAMA. 1979;242:261-4.
7. **Lubin JH, Blot WJ, Berrino F, Flamant R, Gillis CR, Kunze M, et al.** Modifying risk of developing lung cancer by changing habits of cigarette smoking. Br Med J. 1984;288:1953-6.
8. **Hartge P, Silverman D, Hoover R, Schairer C, Altman R, Austin D, et al.** Changing cigarette habits and bladder cancer risk: a case-control study. J Natl Cancer Inst. 1987;78:1119-25.
9. **Ziegler RG.** Vegetables, fruits, and carotenoids and the risk of cancer. Am J Clin Nutr. 1991;53:2515-95.
10. **Koutsky LA, Holmes KK, Critchlow CW, Stevens CE, Paavonen J, Beckman AM, et al.** A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. N Engl J Med. 1992;327:1272-8.
11. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 1998;350:1047-59.
12. **Ziegler RG, Hoover RN, Nomura AM, West DW, Wu AH, Pike MC, et al.** Relative weight, weight change, height, and breast cancer risk in Asian-American women. J Natl Cancer Inst. 1996;88:650-60.
13. **Fearon ER, Vogelstein B.** A genomic model for colorectal tumorigenesis. Cell. 1990;61:759-67.
14. **Grodstein F, Martinez E, Platz EA, Giovannucci E, Colditz GA, Kautzky M, et al.** Postmenopausal hormone use and risk for colorectal cancer and adenoma. Ann Intern Med. 1998;128:705-12.
15. **Schairer C, Adami HO, Hoover R, Persson I.** Cause-specific mortality in women receiving hormone replacement therapy. Epidemiology. 1996;8:59-65.
16. **Barrett-Connor E.** Postmenopausal estrogen and prevention bias. Ann Intern Med. 1991;115:455-6.
17. **Matthews KA, Kuller LH, Wing RR, Meilahn EN.** Prior to use of estrogen replacement therapy, are users healthier than nonusers? Am J Epidemiol. 1996;143:971-8.
18. **Rossouw JE, Finnegan LP, Harlan WR, Pinn VW, Clifford C, McGowan JA.** The evolution of the Women's Health Initiatives: perspectives from the NIH. J Am Med Womens Assoc. 1995;50:50-5.